REMARKS

Claims 1-18, 19 and 21-23 are under consideration. Claims 22 and 23 is amended. Claims 19 and 20 are cancelled. Reconsideration of claims 1-18 and 21-23 is respectfully requested.

Claim Objections

Claim 23 has been amended to correct the informalities. Therefore, this rejection should be withdrawn.

Claim Rejection under 35 USC §112.

Claim 22 is amended to correctly depend on claim 11. Therefore, this rejection should be withdrawn.

Claim Rejections under 35 USC §103

The Action rejected claims 1-13, 15-18 and 21-23 as being unpatentable over Burger et al in view of Constantino et al. The Action states that Burger et al teach a resorbable bone substitute for in vivo implantation comprising bone cement material, an antimicrobial agent (LLLFLLKKRKY) (e.g., claim 23) and albumin as a protein to hold the microbial peptide(s) in solution (page 6, lines 26-32), and that the antimicrobial agent would inherently have a fast release profile. The Action admits that Burger does not teach a bone substitute with TGFβ nor the mixing solutions containing TGFβ and albumin and antimicrobial peptide.

The Action further states that Constantino et al teach aresorbable bone substitute for in vivo implantation, comprising bone cement material, an antimicrobial 9antibiotic) agent, and bone growth factors such as TGF β and albumin (e.g., pages 17-18, page 31, last line pages 32, page 33, lines 1-21), and forming a liquid phase with a protein carrier such as albumin and bone growth factors (see, e.g., page 32, lines 24-28, page 33, lines 1-28 and page 34, lines 1-4, page 35, lines 3-28, page 36, lines 1-12, page 37, lines 1-12). The bone growth factor may be from about 10-50 µg to about 100-500 µg for com^3 of the formulation (e.g., page 35, lines 17-21, page 37, lines 8-12) and

therefore, TGFβhaving a slow release profile would be inherent to the instantly claimed composition.

In response, applicant disagrees because:

First, Burger teaches bone cement comprising antimicrobial peptides, but does NOT describe nor suggest a fast release profile of antimicrobial peptides. Page 1, lines 24-28).

Second, Constantino describes a hydroxyapatite bone cement matrix comprising a biocompatible additive chosen from a large variety of biological molecules, such as a growth factor (claims 11-14), an immunogen (claims 15-19), a vaccine (claims 19-26), anucleic acid (claim 27), a protein (claims 28-29), a cell comprising a gene (claims 30-35), a pharmaceutical agent (claims 36-42), hormones (claims 43-45) and antibiotics (claims 46-56). For delivering antibiotics the dose is given for about 7-14 days and for pharmaceutics- 20 to 30 days (page 30, lines 11-18). In other words, Constantino describes a slow release of antibiotics from bone cement and NOT a fast release antibiotic. Moreover, Constantino does not suggest any combination of compounds.

Third, even the combination of Burger and Constantino does not suggest combining growth factor with an antimicrobial in bone cement with the antibiotic having a fast release characteristic. In fact, Burger describes a slow release antimicrobial peptide (See first paragraph, page 1). Moreover, there was prejudice against the use of antibiotics because of the risk of developing antibiotic resistant microorganisms at the location of insertion of bone cement. This is substantiated in the article by Winniger and Fass, see page 2675, last paragraph- indicating that there are controversies with regard to use of antibiotic. On page 2678, they discuss they discuss the serious risk of having a secondary infection as a result of antibiotic impregnated bone cement. Exhibit 1, enclosed.

In contrast, the present invention uses a fast release antibiotic with a slow releasing growth factor and results in an unexpected synergistic effect of the combination. (See page 19-20, Example 3) This distinguishes the present invention

based on prior art cited , Merck & Co., Inc v. Biocraft laboratories Inc, 874 F2d 804, 10USPQ2d 1843 (Fed Cir 1989). It was not merely a judicious selection of ingredients by a skilled artisan from prior art as argued in the Office Action. As described on Page 4, lines 27-32 and in Figure 4 of the disclosure, the fast release of the antibiotic results in a fast antimicrobial action and cleaning the wound. In addition, the fast release does not allow the microbes to develop resistance as would be the case with a slow release pattern of the antibiotic. The unique characteristic of the present invention is the rapid release and action of the antibiotic to achieve optimal conditions for the host to generate bone material without microbial infection. Therefore, claims 1-13, 15-18 and 21-23 are distinguishable from Burger et al in view of Constantino et al, and the above rejection should be withdrawn.

The Action rejected claims 1-5 and 11-16 as unpatentable over Wang in view of Van Niew Amerongen et al stating that Wang describes a resorbable bone substitute comprising bone cement, antimicrobial (antibiotic0 agent and bone growth factor, but admits that Wang does not explicitly teach SEQ ID NO.4 as antimicrobial, or TGFβ having a slow release profile.

Van Nieuw Amerongen et al was cited because it describes the microbial agent coating apatite/cement implants but did not explicitly describe it having a slow release profile. . The Action concludes that it would be obvious to modify the apatite cement composition of Wang by utilizing the anti microbial agent LLLFLLKKRKKRKY as taught by Van Nieuw Aromgen et al.

In response, applicant respectfully disagrees because Wang does not teach a resorbable bone substitute having an antibiotic having a fast release profile and a bone growth factor having a slow release profile. It is this unique combination that enables the implantation site to be cleaned of microorganisms and for creating conditions to regenerate bone material using a slow release growth factor. The prior art cited does not describe a fast release antibiotic alone or in combination with the slow release bone growth factor, and the statement that the inventive combination of the present invention would be obvious is clearly based on hindsight which is impermissible. Importantly, the present invention provides significantly improved cement, not having the disadvantages

of the antibiotic containing bone cement of the art (the slow release type) that leads to resistance, and providing a unique and improved regenerative ability to the bone cement. Therefore, the above rejection should be withdrawn as a matter of law and fact.

Applicant have made a diligent effort to amend the Claims to allowable form and to respond to the rejections made in the Office Action. Applicants request an interview in person or by telephone to resolve any outstanding issues, should the Examiner deem that this application is not in condition for allowance.

Respectfully submitted,

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